Declaration

CERTIFICATE OF MAILING

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ELI LILLY AND COMPANY

By Kelly Ramsey Date 2-1-02

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Benjamin Lee Hughes, et al.	)
Serial No.	:	09/383,789	)
Filed	:	August 26, 1999	) Group Art Unit: 1653
For	:	Method of Administering Insulintropic Peptides	) Examiner D. Lukton
Docket No.	:	X-12013	)

DECLARATION UNDER 37 C.F.R. 1.132

Assistant Commissioner for Patents
Arlington, VA 22202-0327
Sir:

I, Ronald K. Wolff, of the City of Carmel, County of Hamilton, State of Indiana, hereby state and declare that:

1. I am the co-inventor of the above referenced U.S. Patent Application Serial No. 09/383,789 (hereinafter the '789 Application). I have reviewed the '789 Application and the outstanding Final Rejection (Paper No. 16) for this application.

2. GLP-1 molecules are biologically active polypeptides that have been shown to normalize blood glucose levels in Type II diabetic patients when administered subcutaneously or intravenously. The '789 Application is directed to a method of administering a GLP-1 molecule by pulmonary means.

3. The '789 Application shows that a GLP-1 molecule can be administered to the lungs and that certain antigenic determinants of the peptide appear in the serum. The Examiner states that the immunoassay employed in the '789 Application to ascertain serum concentration, however, "does not establish that the intact peptide appears in the serum." The Examiner questions whether "the GLP-1 molecule exhibits any particular physiological effect at all when administered to the lung."

4. Under my direction, pharmacodynamic data was generated showing that dry powder formulation comprising a GLP-1 molecule administered by inhalation to dogs decreased plasma glucose compared to the sham air exposure without the GLP-1 molecule.

5. The pharmacodynamic data was obtained as follows:
   - A dry powder formulation of Val^{8}-GLP-1(7-37)OH was prepared for inhalation (IH) delivery.
   - A solution formulation of Val^{8}-GLP-1(7-37)OH was prepared for subcutaneous (SC) delivery.
   - Glucose was infused at a rate of 18 mg/kg/min intravenously into three normal non-diabetic Beagle dogs.
   - The three dogs were each dosed with three different dosing regimens on three different days: a) sham air exposure without the Val8-GLP-1(7-

37)OH molecule on the first day; b) IH administration of the dry powder formulation of Val^8-GLP-1(7-37)OH at a mean inhaled dose of 0.85 mg/kg, which resulted in an estimated deposited lung dose of 0.21 mg/kg on a second day; and c) SC administration of the solution formulation of Val^8-GLP-1(7-37)OH at a dose of 0.2 mg/kg on a third day. Blood samples were taken periodically for the determination of plasma glucose.

- The results of the *in vivo* comparison dog study are shown in Table 1 and graphically in Appendix A.

Table 1. Mean Glucose Concentrations (+ SE) in Beagle Dogs Following Sham Air Exposure, IH Administration of the Dry Powder Formulation of Val^8-GLP-1(7-37)OH, or SC Administration of the Solution Formulation of Val^8-GLP-1(7-37)OH

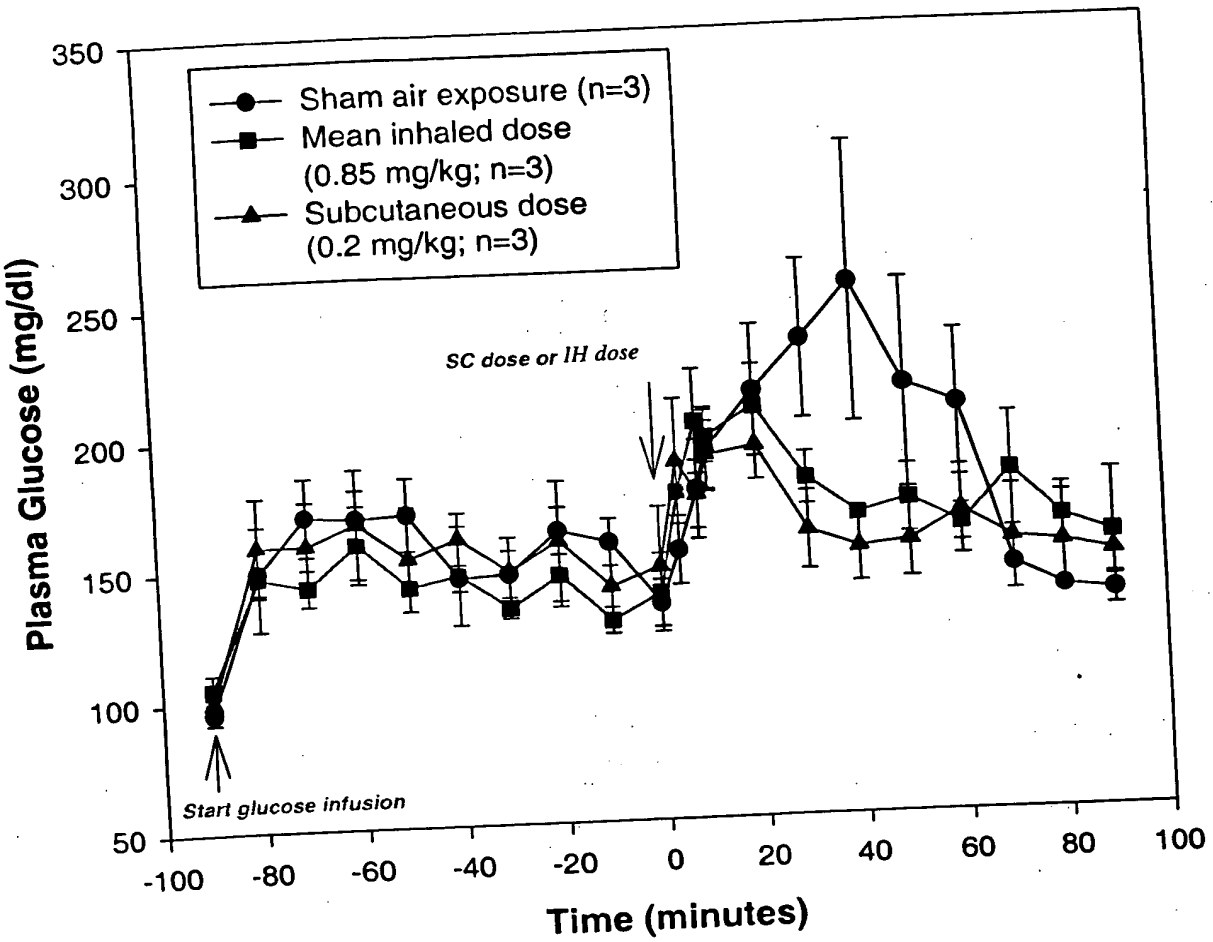
Time (minutes)	Sham	(SE)	IH Formulation	(SE)	SC Formulation	(SE)
-90	96	4	105	6	100	2
-80	149	8	147	20	159	19
-70	170	15	143	7	159	17
-60	169	11	159	15	167	21
-50	170	14	142	9	153	20
-40	145	5	146	19	160	10
-30	146	9	133	4	147	13
-20	162	9	145	12	158	23
-10	157	9	127	5	140	18
0	133	9	137	15	147	23
4	153	13	175	1	187	24
8	176	19	202	20	174	13
10	191	16	196	10	189	13
20	213	25	207	16	192	13
30	232	30	179	10	159	15
40	253	53	165	1	152	13
50	214	40	170	13	154	14
60	206	28	160	7	165	17
70	144	2	180	22	154	20
80	135	2	162	12	152	19
90	133	6	155	24	148	10

6. In view of these data, I conclude:
   a) The dry powder formulation of Val^8-GLP-1(7-37)OH delivered by IH resulted in a clear decrease in plasma glucose, compared to the sham air exposure without the GLP-1 molecule.
   b) This data is consistent and corroborate the immunoassay data and assertions in the '789 Application that GLP-1 molecules administered to the lung and detected in the serum are biologically active and useful as described.

7. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and may jeopardize the validity of the application or any patent issuing thereon.

Ronald Keith Wolff

01 February 2002
Date


Sham air exposure (n=3)
Mean inhaled dose
(0.85 mg/kg; n=3)
Subcutaneous dose
(0.2 mg/kg; n=3)
SC dose or IH dose
Start glucose infusion
Plasma Glucose (mg/dl)
Time (minutes)
350
300
250
200
150
100
50
-100
-80
-60
-40
-20
0
20
40
60
80
100

Appendix A